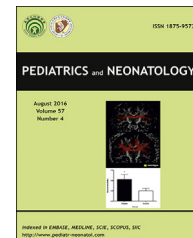


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## BRIEF COMMUNICATION

# Caffeine Toxicity in a Preterm Neonate

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## 1. Introduction

Apnea of prematurity is a common complication in premature infants. The first-line pharmacotherapeutic agent for this condition is caffeine, a methylxanthine. Caffeine is preferred over theophylline because it has fewer adverse effects and a wider therapeutic window.<sup>1</sup> Measuring the serum caffeine concentration is not required in preterm neonates because most of these infants can tolerate therapeutic levels.<sup>2</sup> In this paper, we present the first report of a preterm neonate in whom the serum caffeine concentration exceeded therapeutic levels, which resulted in rhabdomyolysis.

## 2. Case Report

A female infant weighing 1028 g was born at 28 weeks of gestation by cesarean section. Her Apgar scores were 2 at 1 minute and 6 at 5 minutes. She was intubated, administered a single dose of surfactant, and placed on mechanical ventilation for 2 days because of respiratory distress syndrome.

On the 2<sup>nd</sup> day, hemodynamically significant patent ductus arteriosus was diagnosed, based on echocardiography. Treatment was initiated with a starting dose of

0.2 mg/kg intravenous indomethacin, followed by two doses of 0.1 mg/kg at a 24-hour interval.

After extubation, she experienced episodes of apnea on the 3<sup>rd</sup> day. Caffeine therapy was initiated with a bolus dose of 20 mg/kg, followed by daily maintenance doses of 5 mg/kg. On the 8<sup>th</sup> day, the caffeine dose was increased to 9 mg/kg because of recurrent apnea. However, because she developed tachycardia (heart rate, 180 beats per minute), we reduced the caffeine dose to 7 mg/kg on the 12<sup>th</sup> day. Her apnea was well controlled thereafter and caffeine therapy was continued at 7 mg/kg. Her serum creatinine kinase (CK) levels increased from 83 U/L (on Day 6) to 659 U/L (on Day 17). However, she did not exhibit any associated jitteriness or seizure. On the 18<sup>th</sup> day, her urine myoglobin concentration increased to 81.1 ng/mL, whereas her serum caffeine concentration was 32.59 mcg/mL (Figure 1).

She had no history of hypoxia, hypothyroidism, infection, or infarction, any of which could have increased the serum CK levels. Moreover, she had no symptoms or family history of myopathy. The elevated serum CK levels and increased urine myoglobin concentration indicated caffeine-related rhabdomyolysis.<sup>3</sup> After reducing the caffeine dose, her serum CK levels gradually returned to normal, and she had no caffeine-related clinical symptoms.

## 3. Discussion

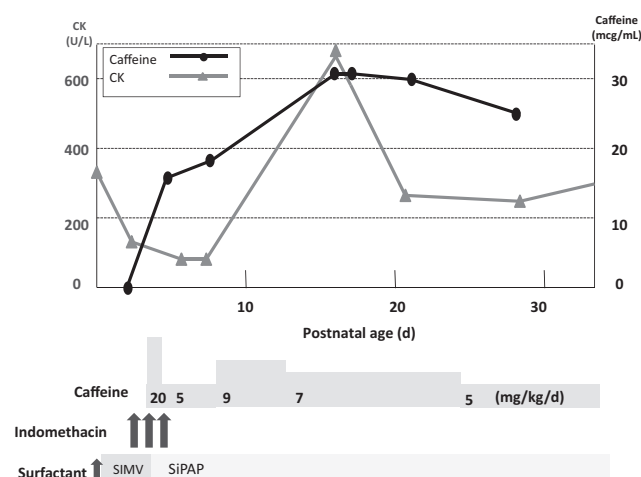
This case of caffeine toxicity in a preterm neonate had two important clinical features. First, the serum caffeine concentration exceeded the therapeutic levels, despite the

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**Figure 1** Clinical course of the patient. CK = creatinine kinase; SIMV = synchronized intermittent mandatory ventilation; SiPAP = synchronized inspiratory positive airway pressure.

administration of the recommended dose. The therapeutic serum caffeine concentration for treating apnea of prematurity is 8–20 mg/mL, whereas the toxic serum concentration is > 50 mg/mL; the half-life of caffeine is 72–96 hours in neonates.<sup>3</sup> In our patient, the half-life of caffeine, calculated from her serum caffeine concentration, was determined as 245.2 hours. Based on this half-life, her serum caffeine concentration was expected to become much higher between the 8<sup>th</sup> day and 17<sup>th</sup> day (Figure 1).

Caffeine is metabolized by the hepatic cytochrome P-450 monooxygenase pathway, but its activity is lower in premature infants than in adults.<sup>4</sup> Therefore, > 85% of the administered caffeine dose is recovered unchanged in the urine of an infant during the 1<sup>st</sup> month of life.<sup>4</sup> A previous study found that caffeine elimination was severely depressed in extremely premature infants for the first 6 weeks after birth.<sup>5</sup> In our patient, caffeine elimination was prolonged because of her prematurity and young age at which the caffeine was first administered. This prolonged elimination could have caused the high serum caffeine concentration.

Second, caffeine administration caused rhabdomyolysis in our patient. The cutoff values of serum CK levels in rhabdomyolysis remain controversial; however, the elevation of serum CK level by more than five-fold is an indicator of rhabdomyolysis.<sup>6</sup> Other frequent reasons for high serum CK levels—myocardial infarction, thyroid dysfunction, muscle injuries, and drugs—were not noted. Several cases<sup>7</sup> of caffeine overdose leading to rhabdomyolysis have been reported in adults; however, there are no reports of

caffeine-related rhabdomyolysis in neonates. Some reports have described caffeine toxicity-related tachycardia, tachypnea, irritability, jitteriness, and vomiting in preterm neonates.<sup>1,3</sup> When caffeine toxicity is suspected, clinicians should assess the serum caffeine concentration and serum CK levels. Caffeine is safely used in neonatal intensive care units, although serum caffeine concentration may exceed therapeutic levels and the additional administration of caffeine may cause rhabdomyolysis in preterm newborns. Further reports should be collated to confirm the correlation between caffeine toxicity and rhabdomyolysis in preterm neonates.

## Conflicts of interest

No contributing authors has any conflicts of interest to declare.

## Acknowledgments

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